b. a second element comprising a translocation element able to facilitate the transfer of a polypeptide across a vesicular membrane in a pancreatic cell, and

c. a third element comprising a therapeutic element able, when present in the cytoplasm of a pancreatic cell, to inhibit or block enzymatic secretion by said pancreatic cell.

REMARKS

Applicants have amended independent claim 1 to indicate that the translocation element of the claimed composition is able to facilitate transport of a polypeptide across a vesicular membrane in a pancreatic cell. This amendment is supported by the specification, e.g., at page 11, lines 11-29.

TRAVERSAL OF EXAMINER'S WITHDRAWAL OF CLAIMS 9-12 AS BEING DRAWN TO A NON-ELECTED INVENTION

The Examiner has withdrawn claims 9-12 as being directed to a non-elected invention. Applicants respectfully request reconsideration of the withdrawal of these claims.

In the April 27, 2000 Office Action, Applicants made a provisional election of species with traverse. The elected species, as accurately set forth by the Examiner in the April 27, 2000 Office Action, was a composition comprising a specific binding element comprising SEQ ID NO: 6, a specific translocation element comprising the N-terminal portion of a *Clostridium botulinum* neurotoxin; a specific therapeutic element cleaving a SNARE protein comprising the light chain of BoNT/A or E cleaving SNAP-25; and a specific spacer moiety comprising a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

Significantly, SEQ ID NO: 6 is an amino acid sequence comprising the carboxy terminus of the pro-CCK peptide. The amino acid sequences SEQ ID NO: 5, 4, 3, and 2 are progressively longer amino acid chains all of which are also contained in the pro-CCK peptide chain. The Examiner has stated that the peptides represented by all these sequences "contain the biologically active C-terminal peptide." April 27, 2000 Office Action at page 2.

Applicants are not certain whether by the phrase, "biologically active" the Examiner means "ability to bind a cell surface marker" or some other biological activity. The activity required of these peptides by the pending claims is the former activity, and all these peptides have in common the ability to bind the CCK A receptor (though not necessarily with identical K_d values).

Thus, it can clearly be seen that the elected species of the invention drawn to a composition comprising (among the other indicated elements) a specific binding element comprising SEQ ID NO: 6 clearly includes compositions containing a specific binding element comprising SEQ ID NO: 5; since the binding element comprises the shorter sequence, it includes within its scope ("reads on") the longer sequence. This species also therefore reads on compositions containing binding elements comprising SEQ ID NO: 4, 3, or 2 as well.

In maintaining the election of species requirement, in the April 27th Office Action the Examiner cited Kreis et al. for the proposition that the peptides of SEQ ID NO: 2 and SEQ ID NO: 6 have different abilities to stimulate afferent nerve discharge. However, it is these peptides' ability to specifically bind pancreatic cell surface markers that is at issue in the elected species. And while these peptides may or may not bind such cell surface markers with the same avidity, it is the fact that they bind, rather than their relative avidities, that is material to the presently pending claims.

Thus, the claimed properties of the polypeptides of SEQ ID No. 2-6 are identical, and their sequences are related in the manner set forth by the Applicants in the previous Reply, which is hereby incorporated herein by reference. For this reason, there can be no question but that the elected species reads on the subject matter of claims 9-12, all of which are compositions wherein the binding element comprises SEQ ID NO:6.

REJECTION UNDER 35 USC §103(a)

Claims 1-8 and 13, 17, and 21 were rejected as allegedly obvious over Foster et al. (WO 9633273) in view of Gaisano et al, *J. Biol. Chem.* 269(25):17062-17066 (1994) and Scheele et al., *Gastroenterology* 92(2):345-353 (1987). Applicants respectfully traverse this rejection.

The present invention is directed to a composition, and methods of using such agent, which comprises a binding element able to specifically bind a pancreatic cell surface marker,

a translocation element able to facilitate transfer of a polypeptide across a vesicular membrane, and a therapeutic element able to inhibit or block enzymatic secretion by a pancreatic cell. In preferred embodiments, the composition comprises certain elements derived from a clostridial neurotoxin.

By contrast, Foster discloses a neural cell-specific chimeric therapeutic polypeptide in which the specificity of the C-terminal region of a clostridial neurotoxin is altered so as to change the specificity of the agent's action from one type of neural cell (motor neurons) to another (sensory afferent neurons). Significantly, the new target cell is, like the original target, a neural cell. Neurons share many fundamental characteristics, and common properties such as the mechanism of endocytosis, the microenvironment of endocytotic vesicles, and the processes of synaptic vesicle formation, migration, and fusion with the plasma membrane would clearly be expected to be similar among neural cells whose function is to relay information by way of the presynaptic release of neurotransmitters.

However the differences in function between neural cells and other types of cells, such as pancreatic cells, preclude assuming that the characteristic properties of neural cells and the mechanisms underlying these properties are shared in such other cell types. In particular, despite its detailed description of many embodiments of the therapeutic peptide, the specification of the Foster reference utterly fails to suggest that such a peptide would be therapeutically functional if targeted to cell types other than neurons, certainly not pancreatic cells.

Gaisano does not cure this deficiency. The Gaisano reference proposes a) that *in vitro* TeTx light chain appears to cleave a subpopulation of a VAMP-2-immunoreactive protein found in a pancreatic zymogen granule membrane fraction, and b) the *in vitro* permeabilization of pancreatic acinar cells with streptolysin O (SLO), followed by treatment of these cells with tetanus toxin light chain, and subsequent measurement of Ca^{++}-stimulated amylase secretion, appears to lessen the appearance of amylase in the media. Gaisano also proposes that zymogen granule membranes contain a protein similar (as determined immunologically) to the VAMP-2 SNARE protein.

However, Gaisano acknowledges it is the only group to have made these findings, *id.* at 17064, col.2, and that other groups have obtained results that directly contradict both of these major conclusions; namely, these other groups found that i) TeT does not inhibit Ca^{++}-stimulated enzyme secretion in permeablized cells (Stechter et al., *Biochem J.* 283: 899-904 (1992)) , and ii) BoTx subtype B (which recognizes and cleaves the same amino acid

sequence within neural VAMP-2 as does TeTx) does not cleave the ZGM-associated VAMP-2-like protein (Braun et al., *J. Biol. Chem.* 269: 5328-5335 (1994). *See id.* at 17064, col. 2 and 17065, col.1.

The person of ordinary skill in the art is charged with knowledge of the entire body of technological literature, including that that might lead away from the claimed invention. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir.1988). Like any reference, Gaisano (both alone and in combination with the other cited references) must be evaluated as a whole for what it fairly suggests to one skilled in the art. Applicants submit that one of ordinary skill in the art would recognize that Gaisano's conclusions conflicted with the findings of at least two other groups. At best, the Gaisano paper would be interpreted by such a person as an invitation to attempt further experimentation. However, an invitation to experiment does not render a claimed invention obvious, *id.* at 1532, and the inherent ambiguity of Gaisano cannot be said to in any way suggest a modification of Foster to arrive at the present claimed compositions. Such a modification can only be inferred by improper hindsight reconstruction of the invention in light of the Applicants' own specification.

Moreover, even assuming *arguendo* that the Gaisano paper's conclusions were not ambiguous in light of the state of the art, Gaisano provides no suggestion that the TeTx light chain could be delivered within pancreatic acinar cells *in vivo*, and therefore adds nothing to the deficiency of Foster.

Scheele et al., describe the response of pancreatic acinar cells when exposed to various concentrations of a CCK analog, caerulein. The authors find that at low and normal caerulein concentrations, there is a dose-dependent increase in zymogen granule exocytosis, with amylase appearing normally in pancreatic juice. However, at high concentrations of caerulein, exocytosis is inhibited. The paper indicates that under such conditions secretory enzymes are either released into the lateral intercellular space or are degraded internally within the cell. Scheele at 352.

For the reasons presented above, neither Foster, Gaisano, nor their combination provide any motivation for making the present invention. The addition of Scheele does not provide the missing motivation.

To the extent that Scheele provides any suggestion concerning a therapeutic for treatment of acute pancreatitis, the paper suggests that over-stimulation of pancreatic cells by caerulein is a cause of the condition. Thus, Scheele states, "supramaximal caerulein or caramylcholine stimulation resulted in the development of acute pancreatitis with pancreatic

edema, inflammation and necrosis." *Id.* The paper thus leaves the suggestion that an appropriate therapy for acute pancreatitis would be competitive partial inhibition of caerulein and/or caramylcholine receptor binding.

The combination of Foster, Gaisano and Scheele in no way suggests the presently claimed compositions. In addition to other deficiencies, there is no indication in the combination of these references that the CCK receptor (which is not named or characterized in Scheele) could provide a means for targeted uptake of a drug similar to that of the presently claimed invention, e.g., a modified neurotoxin. Thus, the combination of the references not only fails to suggest the claimed composition , but none of these references would lead one to believe that the preferred engineered clostridial neurotoxin could be internalized and translocated into the cytoplasm by any cells other than neurons, much less by pancreatic cells in particular. Such a suggestion occurs only in the present specification.

CONCLUSION

For the reasons given above, Applicants respectfully urge the Examiner to reconsider rejection of the pending claims. No fee is thought to be required in connection with this communication; however, if Applicant is in error in this regard please use Deposit Account 01-0885 for payment of any fee that may be due.

Respectfully submitted,

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